The Applicants have amended claim 14, and similarly rejected claims 15 and 16 that depend from claim 14. Claim 14 has been amended to indicate that "memory restoring" compounds includes those that improve an animal's diminished capacity to recall. As described in the specification, p53-deficient mice do not have a learning deficiency, (page 5, lines 13-17). Rather, p53-deficient mice have a diminished capacity to recall, (page 5, lines 24-29). The specification describes an exemplary method whereby p53-deficient mice are subjected to a learning test and then treated with a test compound, (page 10, lines 5-11). The p53-deficient mice then are subjected to the test again, and the test compound is screened for memory restoring activity. In light of the specification, one skilled in the art would recognize that compounds with "memory restoring activity" are those that improve an animal's capacity to recall previously learned information. Therefore, the Applicants contend that one skilled in the art would be apprised of the metes and bounds of the claims, and the Applicants respectfully request reconsideration of the rejection of claims 14-16 under 35 U.S.C. 112, Second Paragraph.

35 U.S.C. 112, First Paragraph

In the Office Action dated July 16, 2002, the Examiner stated:

> Claims 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Applicants respectfully traverse the rejection. The test of enablement "requires a determination of whether th[e] disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use *the claimed invention*." MPEP 2164.01 (emphasis added). The Applicants contend that the specification does enable one skilled in the art to make and use the subject matter of the claims.

The Applicants first note that the claims of the instant application are not drawn to compositions. Rather, the claims of the instant application recite methods for screening compounds with anti-anxiety activity and memory restoring activity. The

recited methods include administering the test compound to an animal with at least one non-functional allele of the p53 gene and determining whether the compound decreases anxiety or restores memory. The Applicants contend that the specification enables one skilled in the art to perform the steps recited within the claims.

The claims recite administering a test compound to an animal. Animal models for screening drugs have been widely used for decades, and one skilled in the art would understand the parameters of administering particular drugs to particular animals, *e.g.*, concentration, administration route, *etc.* Further, one skilled in the art would know how to select test compounds based on the anticipated properties of the compounds.

The claims also recite an animal with at least one non-functional allele of the p53 gene (*e.g.*, a heterozygous p53 mutant (p53 +/-), or a homozygous mutant (p53 -/-)). Many types of animals have been subjected to genetic engineering, and creating a p53-deficient animal would not require undue experimentation. In fact, p53-deficient mice are commercially available.

The claims also recite determining whether a compound decreases anxiety or restores memory. The specification discloses that animals with at least one non-functional allele of the p53 gene demonstrate behavioral disorders such as anxiety and/or memory disorders, as determined by the Open-Field test for assessing anxiety and the Morris swimming pool test for assessing memory. Further, the specification indicates that these tests can be used to test for compounds that are capable of acting on anxiety or memory, (page 10, lines 1-11). In addition, as the enclosed or previously submitted scientific articles indicate, one skilled in the art would know how to use p53-deficient mice in the Open-Field test and the Morris swimming pool test to screen for compounds that are capable of acting on anxiety or memory. For example, Archer *et al.*, Walsh *et al.*, Gershenfeld *et al.*, Morméde & Ramos, and the two publications by Crawley (*i.e.*, "Evaluating anxiety in rodents" and "Behavioral Phenotyping of Transgenic and Knockout Mice") disclose the use of the Open-Field test to study anxiety in mice and rats; and Nalbantoglu *et al.*, Hsiao *et al.*, Lassalle & Wahlsten, Crawley (*i.e.*, "What's Wrong with my Mouse?"), and the two publications by Morris himself disclose the use of the Morris swimming pool test to study memory in mice

and rats. In particular, two of the publications by Crawley disclose behavioral phenotyping of *transgenic and knockout mice* using the Open-Field test and the Morris swimming pool test.

It would not require undue experimentation to use these tests *to screen for compounds* that affect anxiety or memory. For example, one skilled in the art would know (1) that a test compound could be administered to p53-deficient mice and wild type mice; (2) that the behavior of these two groups of mice in the Open-Field test or Morris swimming pool test can be compared to the behavior of p53-deficient mice and wild type mice to which the test compound is not administered; and (3) that if a compound causes p53-deficient mice to behave more like wild type mice, then the compound may affect anxiety or memory.

The Applicants respectfully disagree with the arguments presented by the Examiner in support of the rejection. In the Office Action dated July 16, 2002 the Examiner noted:

> the prior art is silent on whether any compounds exist at all that can overcome the loss of function that the p53 mutations introduced....
>
> There is a high level of unpredictability inherent in using a p53 knockout animal as a model to screen for compounds that modulate anxiety or memory. Much of this unpredictability is due to the virtual lack of knowledge as to how p53 mutations contribute to such behavioral deficits.

While a compound that "overcomes the loss of p53" may not be known in the art, such a compound is not required to practice the recited method. One skilled in the art could practice the recited method by administering test compounds that do not necessarily "overcome the loss of p53." For example, one skilled in the art knows that commonly administered sedatives, which are not recognized as "overcoming the loss of p53," could modulate anxiety in any mice, including p53-deficient mice. Therefore, the recited method may be used to screen for new compounds which affect anxiety or memory but do not necessarily "overcome the loss of p53."

The Applicants also contend that knowledge of how p53 contributes to the observed behavioral deficits is not required to practice the recited method. One skilled in the art could practice the recited method merely by observing a phenotype and modulation of the phenotype by administering test compounds, and knowledge of how p53 specifically contributes to the observed behavioral deficits is not required to practice the recited methods. Phenotypic mouse models are commonly used to screen for drugs without an understanding of the underlying molecular mechanism that contributes to the phenotype. Mice are bred to display a particular phenotype, (*e.g.*, hyper- or hypotensive), to create model systems for screening drugs that modulate the phenotype. For example, Gershenfeld *et al.* disclose a genetic analysis of "[t]wo mouse models *developed for screening anxiolytic drugs*," see abstract at page 1 (emphasis added). Therefore, Gershenfeld *et al.* validates the use of mouse models to screen for drugs that modulate anxiety without an understanding of the underlying molecular mechanism that causes the anxiety. In Applicants' case, any unpredictability in the claimed method "due to the virtual lack of knowledge as to how p53 mutations contributes to the behavioral deficits" would not prevent one skilled in the art from practicing the recited method. Rather, it is sufficient that the observed phenotypes of p53-deficient mice (*i.e.*, anxiety and/or memory disorders), are predictable.

Therefore, in light of all the foregoing arguments, the Applicants contend that the subject matter of the claims are fully enabled by the specification. The Applicants respectfully request reconsideration of the rejection of claims 11-16 under 35 U.S.C. 112, First Paragraph.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 1/16/03

By M. Scott McBride

FOLEY & LARDNER
777 E. Wisconsin Ave.
Milwaukee, WI 53202
Telephone: (414) 297-5529
Facsimile: (414) 297-4900

M. Scott McBride
Attorney for Applicants
Registration No. 52,008

MARKED UP VERSION SHOWING CHANGES MADE

Below are the marked up amended claim(s):

14. (Amended) A method for identifying compounds with memory restoring activity, comprising:

(a) administering a test compound to an animal comprising at least one non-functional allele of the p53 gene, wherein the animal has a diminished capacity to recall, and

(b) determining whether said test compound restores memory in said animal, wherein [in which] test compounds that improve the diminished capacity to recall [restore memory in said animal] are identified as compounds with memory restoring activity.